Incidence and associated premorbid diagnoses of patients with chronic rhinosinusitis

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Background: Chronic rhinosinusitis (CRS) is a prevalent condition with underexplored risk factors.
Objectives: We sought to determine CRS incidence and evaluate associations with a range of premorbid medical conditions for chronic rhinosinusitis without nasal polyps (CRSsNP) and chronic rhinosinusitis with nasal polyps (CRSwNP) using real-world clinical practice data.
Methods: Electronic health records data from 446,480 Geisinger Clinic primary care patients were used for a retrospective longitudinal cohort study for data from 2001-2010. By using logistic regression, newly diagnosed CRS cases between 2007 and 2009 were compared with frequency-matched control subjects on premorbid factors in the immediate (0-6 months), intermediate (7-24 months), and entire observed timeframes before diagnosis.
Results: The average incidence of CRS was 83 ± 13 CRSwNP cases per 100,000 person-years and 1048 ± 78 CRSsNP cases per 100,000 person-years. Between 2007 and 2009, 595 patients with incident CRSwNP and 7523 patients with incident CRSsNP were identified and compared with 8118 control subjects. Compared with control subjects and patients with CRSsNP, patients with CRSwNP were older and more likely to be male. Before diagnosis, patients with CRS had a higher prevalence of acute rhinosinusitis, allergic rhinitis, chronic rhinitis, asthma, gastroesophageal reflux disease, adenotonsillitis, sleep apnea, anxiety, and headaches (all $P < .001$). Patients with CRSsNP had a higher premorbid prevalence of infections of the upper and lower airway, skin/soft tissue, and urinary tract (all $P < .001$). In the immediate and intermediate timeframes analyzed, patients with CRS had more outpatient encounters and antibiotic prescriptions ($P < .001$), but guideline-recommended diagnostic testing was performed in a minority of cases.
Conclusions: Patients who are given a diagnosis of CRS have a higher premorbid prevalence of anxiety, headaches, gastroesophageal reflux disease, sleep apnea, and infections of the respiratory system and some nonrespiratory sites, which results in higher antibiotic, corticosteroid, and health care use. The use of guideline-recommended diagnostic testing for confirmation of CRS remains poor. (J Allergy Clin Immunol 2013;131:1350-60.)

Key words: *Epidemiology, incidence, sinusitis, nasal polyps, risk factors, asthma, rhinitis, nested case-control study, antibiotics, diagnosis*

Chronic rhinosinusitis (CRS) is a prevalent inflammatory condition of the paranasal sinuses that encompasses 2 clinically distinct entities: chronic rhinosinusitis without nasal polyposis (CRSsNP) and chronic rhinosinusitis with nasal polyposis (CRSwNP).[1,2] In this article "CRS" refers to both the CRSsNP and CRSwNP entities. Current estimates with patients' self-reported histories (National Health Interview Survey data) of "sinusitis" report a prevalence of 13% in the United States,[3] and chronicity is defined by the American and European consensus statements as the presence of paranasal sinus inflammation for a minimum of 3 months.[4,5] Prior epidemiologic evidence suggests that CRS is prevalent among patients with asthma, immunodeficiency, and cystic fibrosis,[6,7] but it remains unclear whether CRSsNP and CRSwNP are distinct conditions with unique epidemiologic characteristics. Currently proposed causes for both forms include genetic predisposition, innate immune deficits, acquired pathogens, inhaled allergens or irritants, or systemic adaptive immune dysregulation.[8,9]

Surprisingly, the epidemiology and premorbid conditions associated with the diagnosis of CRS remain underexplored, with most prior relevant studies limited by small sample size, use of specialty-specific patient populations, short observation periods, use of self-reported "sinusitis," failure to distinguish acute and chronic forms of sinusitis, and lack of comparison subjects.[6,10,11] Thus the incidence of CRS and associations of a range of premorbid conditions before the diagnosis of CRS and their relative strengths of association remain unknown. Although a prospective longitudinal study examining childhood and adult determinants of CRS would be ideal, challenges to such an approach include the variable latency period of CRSsNP and CRSwNP, the current lack of knowledge about which specific exposures or populations with high prevalence might be most suitable to study, and time and cost considerations.

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Abbreviations used
CPT: Current Procedural Terminology
CRS: Chronic rhinosinusitis
CRSsNP: Chronic rhinosinusitis without nasal polyps
CRSwNP: Chronic rhinosinusitis with nasal polyps
CT: Computed tomography
EHR: Electronic health record
GERD: Gastroesophageal reflux disease
ICD-9: International Classification of Diseases, 9th Revision
OR: Odds ratio
URI: Upper respiratory tract infection
UTI: Urinary tract infection

The widespread adoption of electronic health records (EHRs) by large health care delivery systems facilitates the ability to longitudinally evaluate the health care use of patients with CRS before and after diagnosis. In this study we analyzed data from the Geisinger Clinic, which serves a large primary care population. The population is representative of the real world of clinical practice in primary care and of the general population in the region. In particular, the Geisinger Clinic has up to 10 years of longitudinal data in the EHR. The goal of this study was to evaluate whether patients who eventually received a diagnosis of CRSsNP or CRSwNP were more likely to have a history of specific premorbid illness when compared with control subjects without chronic sinonasal disease. If such a pattern of premorbid illness exists, the nature of the premorbid diseases, effect, and magnitude of each risk factor could be instructive in improving our understanding of causes and mechanisms and allow for the development of preventive interventions targeted toward at-risk populations. More generally, we also evaluated patterns of health care use and treatment before diagnosis and approaches to diagnosis in this population.

METHODS

Study overview

We used longitudinal data from the EHRs of patients with a Geisinger Clinic primary care provider to first calculate annual incidence rates from 2001-2009 and then complete a nested case-control analysis. The goals were as follows: (1) describe the epidemiology of CRS; (2) compare the prevalence and timing of premorbid illnesses preceding incident CRSwNP and CRSsNP compared with those in control subjects; (3) compare health care and antibiotic use among patients with CRSwNP and CRSsNP compared with that among control subjects; and (4) evaluate computed tomography (CT) and nasal endoscopy use in these general population-representative primary care patients. The control group was group matched on age, sex, and visit frequency to the combined CRS populations. Institutional review boards at both the Johns Hopkins Bloomberg School of Public Health and the Geisinger Health System approved this study.

Study population and design

Data were obtained for 446,480 patients of the Geisinger Clinic who had a Geisinger primary care provider from January 1, 2001, to February 9, 2010. Outpatient encounter EHRs were available over this full timeframe, whereas inpatient records were only available after July 1, 2003. The Geisinger Clinic provides primary care and specialty services through 41 community practice clinics and 4 hospitals in a 31-county region of central and northeastern Pennsylvania. The general population in this area is stable. Census data indicate that with the exception of 2 counties, the out-migration rate is less than 1% per year. The primary care population is representative of the region's population (in an analysis comparing Geisinger Clinic patients with National Health and Nutrition Examination Survey subjects on sociodemographic characteristics, unpublished data).

Data sources

EHR data were obtained on demographics, clinical measures, problem list, medical history, and medication history; encounters (eg, office visits, hospitalizations, nurse encounters, telephone inquiries, and specialty consultations); orders (eg, medications, imaging, and procedures); imaging (eg, magnetic resonance imaging, CT, and radiography); and associated International Classification of Diseases, 9th Revision (ICD-9), codes (and, when used, Geisinger System [EP] codes). Current Procedural Terminology (CPT) codes were used to record encounters and procedures.

Identification of patients with CRSsNP, patients with CRSwNP, and control subjects

For the longitudinal study, diagnosed cases occurring between the years 2001 and 2009 were identified for chronic rhinosinusitis (CRSsNP, ICD-9 473.X) and chronic rhinosinusitis with nasal polyps (CRSwNP, ICD-9 471.X). A patient was defined as having an incident diagnosis of CRS during the first year a CRS ICD-9 code was recorded in the patient's outpatient/inpatient/emergency department records. Incident cases of CRSwNP were included regardless of prior presentation with CRSsNP and recorded only in the first year CRSwNP was diagnosed. Patients with CRSsNP could not have a prior or subsequent CRSwNP diagnosis throughout the observed duration of the study. For the case-control study, newly diagnosed incident cases of CRSwNP (595 cases) and CRSsNP (7523 cases) were defined by using ICD-9 codes within the Geisinger Clinic EHR for the years 2007-2009. The analysis was constrained to the post-2007 period to allow for the potential existence of a full 5 years of patients' records within the EHR before the patient's first presentation with CRS. A comparison control group of 8118 outpatient encounters was frequency matched to the combined CRSsNP and CRSwNP group on age strata, sex, and visit year.

Analysis of premorbid conditions and health care use variables

A committee comprised of 4 otolaryngologists and 4 allergists-immunologists identified a list of conditions and corresponding ICD-9 codes relevant to patients with CRSsNP and patients with CRSwNP, along with several comparison conditions (see Table II for codes identified). Premorbid conditions were analyzed for 3 separate time periods before CRS diagnosis or the matched control visit: the total duration under observation (2001-2009) and the immediate (0-6 months) and intermediate (7-24 months) time periods before the CRS diagnosis. Premorbid diagnoses entered during the observed period were identified by their ICD-9 codes. Because this dataset was analyzed retrospectively and examines health care use at a population level, professional society criteria were not used to define symptom complexes, such as asthma and gastroesophageal reflux disease (GERD).

For these time periods, the number of outpatient, inpatient, and emergency department encounters for any indication were compared between cases and control subjects. For medications, a list of orally administered antibiotics, nasally administered corticosteroids, and orally administered corticosteroids was created, and the indications associated with each prescribed antibiotic were compared. The use of sinus CT scans and airway endoscopy for diagnosis was evaluated. We defined the use of airway endoscopy as any patient who had a diagnostic nasal endoscopy (CPT 31231), flexible laryngoscopy (CPT 31575), or endoscopic nasopharyngoscopy (CPT 92511) for any indication. A sinus CT scan was identified with CPT code 70486. For these diagnostic tests, we evaluated from 1 year before to 3 months after CRS diagnosis.

Statistical analysis

For incidence data, any patient with an inpatient or outpatient encounter in a given calendar year contributed 1 person-year to the incidence rate denominator. Rates are presented as the number of incident cases per

100,000 person-years. In unadjusted analyses the 2 case groups and control subjects were compared on demographics, health care use, premorbid conditions, and antibiotic use. SPSS software (SPSS, Inc, Chicago, Ill) was used for contingency tables (χ^2 test) for categorical variables and 1-way ANOVA (F-test) for continuous variables. Polytomous logistic regression was used to compare patients with CRSwNP and patients with CRSsNP with control subjects to adjust for potential confounding variables in evaluating associations with premorbid conditions. For the latter, we adjusted for age (<18, 40 to <50, 50 to <60, 60 to <70, and ≥70 years and older), sex, and race/ethnicity (white and nonwhite). Additional logistic regression models were used to analyze the entire CRS group with a dummy variable in the model for age less than 14 years, continuous age, and cross-products with comorbidities to evaluate effect modification by age on associations of premorbid conditions with CRS status. Comorbidities were added to the base model one at a time, and adjusted odds ratios (ORs) with 95% CIs are provided. Because of the large number of comparisons in this study, we considered a conservative P value of less than .0005 to define statistical significance but did not adjust P values for multiple comparisons. Logistic regression was carried out with Stata version 11.2 software (StataCorp, College Station, Tex).

RESULTS

Description of study population and annual incidence

Data on 307,381 patients who received care at any time in the years 2007, 2008, and 2009 were analyzed to identify 595 incident CRSwNP cases, 7523 incident CRSsNP cases, and 8118 matched control subjects (Table I). The average incidence rate from 2007-2009 was 83 ± 13 CRSwNP cases per 100,000 person-years and 1048 ± 78 CRSsNP cases per 100,000 person-years. Comparing the study time period 2007-2009 with 2001-2006, the incidence of CRSsNP was stable, whereas the incidence of CRSwNP appeared to decrease ($P = .04$, Fig 1). However, because 2001 was the first year EHRs were used widely in the Geisinger Clinic, the incidence data presented in the earlier years likely represent both incident and prevalent CRS cases. The patients with CRSwNP were older and more likely to be male compared with the patients with CRSsNP and control subjects (all $P < .0005$). Season was not associated with CRSwNP onset but was highly significant for CRSsNP onset: adjusted ORs relative to winter for spring, summer, and fall were 1.2 (95% CI, 0.9-1.4), 0.8 (95% CI, 0.6-1.0), and 1.0 (95% CI, 0.8-1.3), respectively, for CRSwNP and 0.8 (95% CI, 0.7-0.9), 0.6 (95% CI, 0.5-0.6), and 0.9 (95% CI, 0.8-1.0), respectively, for CRSsNP. Consistent with the general population in the region, patients were predominantly white; there were no significant differences in race/ethnic composition by group. The average duration from first encounter in the Geisinger Clinic to CRS diagnosis or index visit among cases and control subjects was approximately 5 years.

Associations of premorbid conditions with CRS diagnosis

After adjusting for age, sex, and race, there were large differences in the occurrence of a variety of premorbid conditions among the 3 patient groups but especially for airway diseases (Fig 2 and Table II). Additional analysis adding season of diagnosis into the model was performed, but this did not change the reported associations, and these data are not discussed further. Acute rhinosinusitis, allergic rhinitis, chronic rhinitis, and symptoms of postnasal drip/wheeze/cough/shortness of breath were each associated with subsequent diagnosis of CRS (all $P < .0005$). Asthma was strongly associated with subsequent diagnosis of both CRSsNP and CRSwNP, but the association was strongest with CRSwNP. Additionally, GERD, adenotonsillitis, sleep apnea, and otitis media were associated with a subsequent CRS diagnosis, whereas upper respiratory tract infections (URIs), influenza, pneumonia, and bronchitis were each associated with subsequent diagnosis of CRSsNP (all $P < .0005$). Interestingly, conjunctivitis, atopic dermatitis, urinary tract infections (UTIs), and skin/soft tissue infections were similarly associated with subsequent diagnosis of CRSsNP (all $P < .0005$).

In adjusted models individual systemic or regional autoimmune or autoinflammatory diseases were not associated with subsequent diagnosis of CRS, although, in combination, CRSsNP was associated with autoimmune conditions. Similarly, diabetes and obesity were not associated with subsequent CRS diagnosis. Interestingly, even after adjusting for age and sex, pregnancy (using its ICD-9 code) was associated with decreased odds of CRS diagnosis. Anxiety and headache disorders were associated with increased odds of CRS diagnosis (all $P < .0005$), but depression was not. None of our comparison conditions that were not hypothesized to be risk factors for CRS (ie, hypertension, hypothyroidism, and heart failure) were associated with its subsequent diagnosis.

Timing of premorbid illness

Because CRS is symptomatically defined by the persistence of symptoms for more than 3 months, we analyzed the timing of premorbid illness to separate the symptomatic prodrome expected for CRS. We compared associations in 2 separate periods: the immediate (0-6 months) and intermediate (7-24 month) periods preceding CRS diagnosis (Table III). Expected and definitional diagnoses of conditions, such as rhinitis, acute rhinosinusitis, and URIs, as well as component symptoms, such as headaches and postnasal drip, were acutely increased in the immediate period preceding CRS diagnosis (all $P < .0005$). However, similar associations were also consistently observed for these conditions in addition to asthma, atopic dermatitis, otitis media, and GERD in the intermediate timeframe preceding diagnosis (all $P < .0005$). Significant associations between CRSsNP and adenotonsillitis, bronchitis, pneumonia, conjunctivitis, UTIs, and tobacco were also found in the intermediate timeframe preceding diagnosis (all $P < .0005$).

Comparison of premorbid associations in children and adults

We next examined effect modification by age (<14 vs ≥14 or more years) on the association of premorbid conditions with CRS case status. During the entire observed period, there was only evidence that age modified the association of preceding asthma with CRS case status ($P < .0005$), with a stronger association in the younger group: for persons younger than 14 years, the OR was 2.62 (95% CI, 2.09-3.17), and for persons 14 years and older, the OR was 1.67 (95% CI, 1.52-1.84). When the effect of age was examined in the immediate (0-6 months) timeframe preceding CRS diagnosis, the association of asthma strengthened in both groups but particularly in the pediatric group with age less than 14 years ($P < .0005$): for persons younger than 14 years, the OR was 4.72 (95% CI, 3.40-6.56), and for persons 14 years and older, the OR was 2.32 (95% CI, 2.02-2.67). In the intermediate timeframe (7-24 months before CRS), there was evidence that age modified

TABLE I. Characteristics of the patients with CRSwNP (471.X), patients with CRSsNP (473.X), and control subjects

Characteristic	Patients with CRSwNP	Patients with CRSsNP	Control subjects	*P* value*	Eligible patients
No.	595	7,523	8,118		307,381
Age at diagnosis (y), mean (SD)	48.4 (19.1)	40.3 (22.9)	41.0 (23.0)	<.0005	37.9 (24.0)
Age distribution (y), no. (%)					
0-14	25 (4.2)	1,358 (18.1)	1,426 (17.6)	<.0005	70,157 (22.8)
15-24	52 (8.7)	739 (9.8)	748 (9.2)	.353	42,448 (13.8)
25-34	67 (11.3)	861 (11.4)	928 (11.4)	.991	30,846 (10.0)
35-44	100 (16.8)	1,186 (15.8)	1,286 (15.8)	.799	37,073 (12.1)
45-54	137 (23.0)	1,265 (16.8)	1,402 (17.3)	.001	41,609 (13.5)
55-64	81 (13.6)	983 (13.1)	1,064 (13.1)	.93	35,385 (11.5)
65-74	80 (13.5)	636 (8.5)	636 (7.8)	<.0005	24,321 (7.9)
>75	53 (8.9)	595 (5.6)	628 (7.7)	.577	25,542 (8.3)
Sex, no. (%)					
Female	271 (45.5)	4,377 (58.2)	4,648 (57.3)	<.0005	164,820 (53.6)
Male	324 (54.5)	3,146 (41.8)	3,470 (42.7)	<.0005	142,545 (46.4)
Race/ethnicity (% white)	96.3	94.6	94.3	.12	93.1
Year of diagnosis					
2007 (%)	186 (31.2)	2,390 (31.7)	2,576 (31.7)		225,433
2008 (%)	212 (35.6)	2,411 (32.0)	2,623 (32.3)		237,127
2009 (%)	197 (33.1)	2,722 (33.1)	2,919 (36.0)		250,866
Observed duration† (d), mean (SD)	1,847 (954)	1,775 (970)	1,816 (940)		

*For continuous variables, *P* values are based on 1-way ANOVA for differences between means; for categorical variables, *P* values are based on the Pearson χ^2 test for association.
†The observed duration was the number of days between the first encounter in the Geisinger Clinic system and the date of diagnosis.

the association of a GERD diagnosis, with a much stronger association in the younger group: for persons younger than 14 years, the OR was 3.67 (95% CI, 2.51-5.38), and for persons 14 years and older, the OR was 1.62 (95% CI, 1.47-1.78). The associations of other analyzed conditions, including adenotonsillitis, headache, and otitis media, did not show significant modification by age during any of the observed timeframes.

Health care visit use

Given the pattern of premorbid conditions observed, we next evaluated the patterns of health care use in patients with CRSwNP, patients with CRSsNP, and control subjects (Table IV). In the intermediate timeframe preceding their diagnosis, patients with CRSwNP and patients with CRSsNP used an average of 5.8 and 6.6 outpatient visits, respectively, compared with 5.1 visits in control subjects (all $P < .0005$). In the immediate timeframe preceding their diagnosis, they used 2.6 and 2.9 outpatient visits, respectively, compared with 1.8 outpatient visits in control subjects (each $P < .0005$). Patients with CRSsNP also used more inpatient and emergency department visits than control subjects during both the 6 months preceding their diagnosis and the prior intermediate interval.

Medication use

Patients who subsequently received a diagnosis of CRS were more likely than control subjects to have received an antibiotic both in the immediate and intermediate timeframe preceding diagnosis (Table V). Patients with CRSsNP received an average of 2.7 orders for antibiotics, patients with CRSwNP received 2.4 courses of antibiotics, and control subjects received 1.2 courses of antibiotics in the 24 months before the index visit ($P < .0005$). The patients with CRSwNP and those with CRSsNP were significantly more likely than control subjects to receive an antibiotic in both timeframes examined (for 0-6 months: 43.0%, 54.0%, and 22.3%, respectively; for 7-24 months: 53.8%, 59.5% and 42.3%, respectively; all $P < .0005$). The number of nasal and systemic corticosteroid orders was higher among patients with CRSwNP and patients with CRSsNP in both timeframes (both $P < .0005$). It is interesting to note that the number of antibiotic orders was more than twice that of systemic or nasal corticosteroids in all timeframes analyzed.

The most common indication for antibiotic prescription in all 3 groups, regardless of timeframe, was acute rhinosinusitis. Even in the control group, 7.2% and 16.3% of all patients had received an antibiotic for acute rhinosinusitis in the immediate and intermediate preceding timeframes, respectively. This was significantly higher than for the second and third most common indications, specifically otitis media (2.2% and 6.3% in the immediate and intermediate periods) and bronchitis (3.2% and 8.3% in the same 2 periods). In the immediate period before the CRS diagnosis, the ORs, compared with control subjects, for receiving an antibiotic for acute rhinosinusitis were 4.6 (95% CI, 3.8-5.7) in patients with CRSwNP and 7.5 (95% CI, 6.2-8.2) in patients with CRSsNP. In the intermediate period these associations for acute rhinosinusitis were 2.4 (95% CI, 2.0-2.8) in patients with CRSwNP and 2.9 (95% CI, 2.7-3.1) in patients with CRSsNP. In addition to acute rhinosinusitis, patients with CRS were also more likely to have received an antibiotic for bronchitis, acute pharyngitis, and an acute URI.

Use of diagnostic testing

We further evaluated the use of recommended confirmatory diagnostic tests (nasal endoscopy or a sinus CT scan, Table VI).[4,5] The use of these diagnostic modalities was evaluated in 3 time intervals: (1) "ever" if the modality had ever been used; (2) 0 to 12 months before diagnosis; and (3) up to 3 months after diagnosis. Patients with CRSwNP were more likely than patients with CRSsNP and control subjects to have been evaluated with nasal endoscopy or a sinus CT scan (51.8%, 24.2%, and 3.6%,

TABLE II. Associations of provider-coded diagnoses with CRS case status during the entire observed duration before diagnosis of CRSwNP (471.X) and CRSsNP (473.X)

Premorbid condition	ICD-9 codes used	Patients with CRSwNP, no.	Patients with CRSsNP, no.	Control subjects, no.	Patients with CRSwNP vs control subjects, aOR (95% CI)	Patients with CRSsNP vs control subjects, aOR (95% CI)
Upper airway (combined)†		486 (81.7)	6,451 (85.8)	5,627 (69.3)	2.2 (1.8-2.8)*	2.7 (2.5-2.9)*
Acute rhinosinusitis (%)	461.X	339 (57.0)	5,061 (67.3)	3,191 (39.3)	2.2 (1.8-2.6)*	3.2 (3.0-3.4)*
Otitis media (%)	382.X	102 (17.1)	1,871 (24.9)	1,364 (16.8)	1.8 (1.4-2.2)*	1.8 (1.6-1.9)*
Acute URI (%)	460, 462, 463, 464.X, 465.X	266 (44.7)	4,247 (56.5)	3,609 (44.5)	1.3 (1.1-1.5)	1.6 (1.5-1.8)*
Allergic rhinitis (%)	477.X	254 (42.7)	3,071 (40.8)	1,841 (22.7)	2.6 (2.2-3.1)*	2.4 (2.2-2.5)*
Chronic rhinitis (%)	472.0	124 (20.8)	1,325 (17.6)	578 (7.1)	3.5 (2.8-4.4)*	2.8 (2.5-3.1)*
Postnasal drip/wheeze/cough (%)	784.91, 786.05,07,2	175 (29.4)	2,786 (37.0)	1,946 (24.0)	1.5 (1.2-1.8)*	1.9 (1.8-2.0)*
Adenotonsillitis (%)	474.0X, 474.1X	11 (2.9)	227 (3.0)	100 (1.2)	2.6 (1.3-4.9)*	2.5 (1.9-3.1)*
Sleep apnea	327.2X	22 (3.7)	156 (2.1)	110 (1.4)	2.2 (1.4-3.5)*	1.6 (1.2-2.0)*
Lower aerodigestive tract (combined)†		342 (57.5)	4,656 (61.9)	3,848 (47.4)	1.5 (1.2-2.7)*	1.8 (1.7-2.0)*
Asthma (%)	493.X	142 (23.9)	1,369 (18.2)	916 (11.3)	2.8 (2.3-3.5)*	1.7 (1.6-1.9)*
Cystic fibrosis (%)	277.0X	6 (1.0)	4 (0.1)	0 (0.0)	NC	NC
Pneumonia (%)	480-6, EP458-9, 770	44 (7.4)	761 (10.1)	505 (6.2)	1.3 (0.9-1.7)	1.7 (1.5-1.9)*
Bronchitis (%)	466.X, 490, EP275	212 (35.6)	3,334 (44.3)	2,509 (30.9)	1.2 (1.0-1.4)	1.7 (1.6-1.8)*
GERD (%)	530.81, EP699	176 (29.6)	2,220 (29.5)	1,666 (20.5)	1.5 (1.2-1.8)*	1.7 (1.6-1.8)*
Influenza (%)	487.X, 488.X	26 (4.4)	292 (3.9)	239 (2.9)	1.6 (1.1-2.4)	1.3 (1.1-1.6)
Epithelial conditions (combined)†		192 (32.3)	2,700 (35.9)	2,410 (29.7)	1.2 (1.0-1.4)	1.3 (1.2-1.4)*
Conjunctivitis (%)	372.0-2X	29 (4.9)	471 (6.3)	314 (3.9)	1.6 (1.0-2.3)	1.6 (1.4-1.9)*
UTI (%)	599	70 (11.8)	941 (12.5)	796 (9.8)	1.3 (1.0-1.7)	1.3 (1.2-1.5)*
Atopic dermatitis (%)	691.8	25 (4.2)	369 (4.9)	291 (3.6)	1.7 (1.1-2.5)	1.4 (1.2-1.6)*
Psoriasis (%)	696.1	14 (2.4)	145 (1.9)	131 (1.6)	1.2 (0.7-2.2)	1.2 (1.0-1.5)
Inflammatory bowel disease (%)	555.X, 556.X	8 (1.3)	101 (1.3)	83 (1.0)	1.1 (0.5-2.3)	1.3 (1.0-1.7)
Skin/soft tissue infections (%)	035, 680.X, 681.X, 682.X, 684, 686.9	99 (16.6)	1,370 (18.2)	1,301 (16.0)	1.0 (0.8-1.3)	1.2 (1.1-1.3)*
Systemic autoimmune disease (combined)†		9 (1.5)	145 (1.9)	100 (1.2)	1.2 (0.6-2.4)	1.6 (1.2-2.1)*
Systemic lupus erythematosus (%)	710.0, EP212-7, EP611, EP621	3 (0.5)	26 (0.3)	13 (0.2)	3.6 (1.0-12.8)	2.2 (1.1-4.3)
Rheumatoid arthritis (%)	714.X	7 (1.2)	121 (1.6)	89 (1.1)	1.0 (0.5-2.2)	1.5 (1.1-2.0)
Other selected general medical conditions (combined)†		162 (27.2)	1,887 (25.1)	2,066 (25.5)	1.0 (0.8-1.2)	1.0 (0.9-1.1)
Diabetes mellitus (%)	250.X, EP205,206	64 (10.8)	741 (9.8)	862 (10.6)	0.8 (0.6-1.0)	1.0 (0.9-1.1)
Obesity (%)	278.01-2; EP8902V85.3x,4,5x; 649.1x,	90 (15.1)	947 (12.6)	954 (11.8)	1.2 (1.0-1.6)	1.0 (0.9-1.2)
Tobacco use (%)	305.1X, 649.0-4, 989.84	29 (4.9)	329 (4.4)	271 (3.3)	1.2 (0.8-1.9)	1.3 (1.1-1.6)
Pregnancy (%)	650, 651.x, V22.x,V23.x,V27.x	17 (2.9)	325 (4.3)	431 (5.3)	0.6 (0.4-1.0)	0.7 (0.6-0.9)*
Selected neuropsychiatric conditions (combined)†		192 (32.3)	2,229 (29.6)	1,573 (19.4)	1.9 (1.6-2.3)*	1.8 (1.7-1.9)*
Anxiety (%)	300.0X	42 (7.1)	482 (6.4)	316 (3.9)	1.7 (1.2-2.4)	1.7 (1.5-2.0)*
Depression (%)	311	32 (5.4)	400 (5.3)	354 (4.4)	1.1 (0.8-1.6)	1.3 (1.1-1.5)
Headache (%)	339.X, 346.X, 784.0	162 (27.2)	1,846 (24.5)	1,235 (15.2)	2.1 (1.7-2.6)	1.8 (1.7-2.0)*
Other comparison conditions (combined)†		235 (39.6)	2,511 (33.4)	2,681 (33.0)	1.0 (0.8-1.2)	1.1 (1.0-1.2)
Hypothyroidism (%)	244.X	67 (11.3)	830 (11.0)	788 (9.7)	1.1 (0.8-1.4)	1.1 (1.0-1.3)
Colon cancer (%)	153.X	6 (1.0)	30 (0.4)	48 (0.6)	1.3 (0.5-3.1)	0.7 (0.4-1.1)
Essential hypertension (%)	401.X	198 (33.3)	2,086 (27.7)	2,255 (27.8)	0.9 (0.7-1.1)	1.0 (0.9-1.1)
Heart failure (%)	428.0	19 (3.2)	206 (2.7)	213 (2.6)	0.9 (0.5-1.5)	1.1 (0.9-1.3)

aOR, Adjusted odds ratio; *NC*, models did not converge.
*$P < .0005$: logistic regression was used to derive adjusted ORs and 95% CIs, controlling for race/ethnicity, sex, and age.
†Contains the combined prevalence and adjusted ORs of all diagnoses listed under each category.

respectively; all $P < .0005$). Patients were more frequently evaluated with endoscopy or a CT scan in the 3 months after diagnosis than in the 1 year prior.

DISCUSSION

In this study we used 10 years of data from a large cohort of primary care patients from the EHRs of the dominant health care provider serving an expansive geographic region to evaluate the epidemiology of CRS, test several previously proposed hypotheses regarding the pathobiology of CRS, and examine how CRS is being treated and diagnosed in the community. To our knowledge, this study has provided the first estimate of the incidence of physician-diagnosed CRS. Our study shows a remarkable pattern of episodic and chronic airway illnesses preceding diagnosis of both CRS subtypes, lending support to the notion of the unified airway linked by common physiologic and pathologic responses in both the upper and lower airways. Although the association of

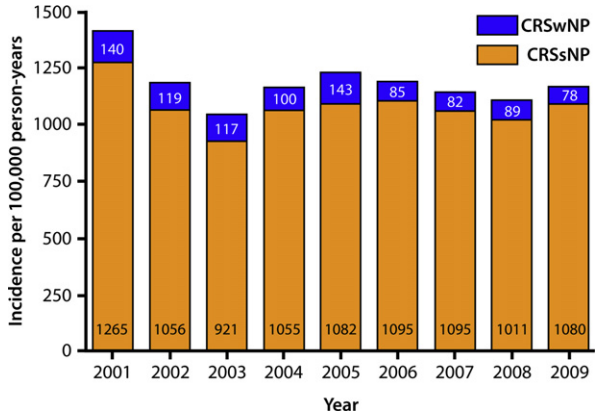

FIG 1. Incidence of CRSwNP and CRSsNP from 2001-2009 in the Geisinger Clinic of patients with a Geisinger primary care provider.

airway diseases with subsequent diagnosis of CRS was strongest in the 0 to 6 months immediately before diagnosis, this pattern extended to the prior 7 to 24 months before diagnosis. These findings further suggest that acute episodic respiratory diseases can modify host susceptibility to CRS, perhaps similarly to the relationship between rhinovirus and respiratory syncytial virus infections and subsequent asthma development.[12,13] Additionally, we show that there are modest but highly significant associations between premorbid infections at other nonrespiratory sites, GERD, and sleep apnea, anxiety, and headache disorders among patients subsequently given a diagnosis of CRS. Although there was a strong magnitude of association between autoinflammatory/autoimmune conditions, our study might still be underpowered to study the associations with relatively rare conditions, such as autoimmunity. In our analysis of health care practice patterns preceding CRS diagnosis, we find that patients who developed CRS used antibiotics, nasal and systemic corticosteroids, and outpatient and inpatient health care services more frequently than control subjects and that CRS is commonly diagnosed without the use of confirmatory diagnostic testing, such as nasal endoscopy or sinus imaging.

The strengths of this study include the use of physician-coded diagnoses entered at the time of the encounter. This is likely a more accurate record of premorbid illness than patient recall, which was typically used in most previous studies of premorbid risk factors in patients with CRS.[7,14,15] This study was performed in an area of remarkable population stability, encompassed patients receiving care in a variety of settings, and is less susceptible to referral bias than most specialty-based studies of CRS. Furthermore, patients in this study had been under observation for a median duration of approximately 5 years and included a precedent timeframe well in excess of the symptomatic prodrome expected for CRS. The length of observation also enabled us to examine for associations and use trends preceding CRS that could not be examined in prior epidemiologic studies using the episode-based sampling methodology of the National Ambulatory Medical Care Survey to study CRS.[16,17] Finally, we were also able to compare our findings with an age-, sex-, and visit-matched population to evaluate associations and their magnitude with the premorbid illnesses studied. Although interpretation of epidemiologic data is dependent on both the magnitude of association and the precision of the estimate, we chose to focus discussion on results significant at a very conservative P value (<.0005). To our knowledge, this study represents the first nonspecialty care–based, population-representative, case-control study examining the premorbid diagnoses and health care use of patients with CRS.

Our study was able to redemonstrate previously known demographic risk factors for CRSwNP, namely male sex and increased age.[18,19] Our study also expands on previous findings that patients with CRS have more frequent exacerbations in winter[20] and demonstrates that the winter and fall seasons were strongly associated with incident CRSsNP diagnosis but not with CRSwNP. We affirm that diseases previously thought to be risk factors for the development of CRS, such as asthma[21] and allergic rhinitis,[22] have a large and significant association with subsequent diagnosis and further show that asthma, in particular, is a stronger risk factor in children compared with adults. This supports previous studies that have shown that between 70% and 88% of asthmatic patients report sinonasal symptoms[23] and that patients with CRSwNP are more likely to have concurrent asthma.[24,25] Although atopy is frequently cited as a risk factor for CRS,[22] the relationship between atopy and CRS is underexplored at the population level and is complicated by factors including an intrinsic bias among patients tested for atopy, the uncertain significance of individual skin test or RAST test positivity, and variation in the panels used for atopic testing.[26] Nonetheless, high rates of atopy are detected among patients with CRS,[19] there are parallels between the gene transcription program of nasal polyps and skin from atopic dermatitis,[27] and there appears to be a physiologic relationship between positive nasal challenge results and sinus inflammation.[28] Similarly, a longitudinal case-control study of Navy aircrew also demonstrated that there was a statistically significant increase in the number of cases of CRS in subjects with a history of allergic rhinitis.[29]

Our study finds dramatic associations between expected conditions of the upper airway, such as chronic rhinitis, acute sinusitis, and postnasal drip, but also finds an increased premorbid risk of several acute and chronic inflammatory conditions of the middle ear and lower airway. Otitis media, adenotonsillitis, pneumonia, and bronchitis were each modestly but significantly associated with subsequent diagnosis of CRSsNP in both adults and children. Similar associations were observed for patients with CRSwNP, but results did not achieve statistical significance, possibly because of the substantially smaller size of the CRSwNP group. These findings provide strong support for a unified airway concept in which the mucosal surfaces of the upper and lower airways, including the middle ear and the Waldeyer ring, likely share common pathogens and mechanisms of inflammation and innate immunity.[30,31] Given the success of vaccination for the prevention of pneumonia and influenza, these findings raise the possibility that prophylactic vaccination might find efficacy in the prevention of CRS.

In addition to airway conditions, our study finds a relatively strong and significant association between sleep apnea and GERD in both groups of patients with CRS. The association with GERD was significant across all timeframes preceding diagnosis, whereas for sleep apnea, separating the analysis into 2 separate time periods reduced the power to detect a significant association. When the effect of age on the association of GERD and CRS was analyzed, we found that age strengthened the association between GERD and CRS diagnosis, particularly in children. The relationship between GERD and sinusitis is controversial, but several large epidemiologic case-control studies of adults and children have consistently demonstrated an association between GERD

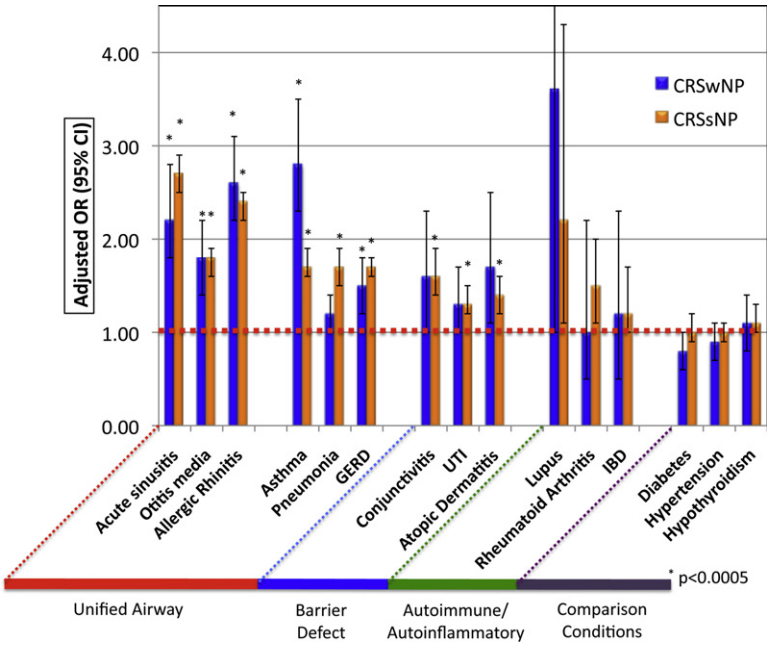

FIG 2. Adjusted associations comparing patients with CRSwNP and patients with CRSsNP with control subjects *(dotted red line)* by using selected provider-coded diagnoses for the entire observed duration before CRS diagnosis. *IBD,* Inflammatory bowel disease.

and sinusitis.[32,33] Furthermore, the European Community Respiratory Health Study, a multinational longitudinal study, has suggested that GERD, particularly nocturnal GERD, is strongly associated with the development of lower respiratory tract diseases, such as asthma, but has not specifically examined its effect on sinusitis.[34,35] These studies have similarly found that nocturnal GERD is frequently comorbid with sleep apnea, whereas more recent analyses suggest that GERD precedes the onset of both sleep apnea and respiratory symptoms.[36] Together with our findings, these studies could suggest that GERD, possibly in parallel with comorbid sleep apnea, might play an important but underrecognized role in the pathogenesis of CRS, perhaps through direct mucosal injury from refluxed or aerosolized acid. Evidence for antireflux therapy in treating CRS is limited but has been studied in several small series previously reviewed by Dibaise and Sharma[37] and represents a possible preventive option that requires further study. Unfortunately, because the ICD-9 codes for laryngopharyngeal reflux and other extraesophageal manifestations of GERD are shared with other nonspecific diagnoses, we were limited in our ability to assess the effect of these condition on CRS.

A significant association between CRS and infectious and inflammatory conditions outside the airway has not been reported for immunocompetent subjects (premorbid diagnosis of an acquired ICD-9 042 and 043 or primary ICD-9 279.X immunodeficiency were rare in this population [<10 subjects total per ICD-9 code]), but our study shows a modest but significant association between conjunctivitis, atopic dermatitis, skin/soft tissue infection, and UTI among patients with CRS. Although these relatively modest associations might reflect our high study power, we believe that these findings do reflect a biologically meaningful association between an impaired host epithelial barrier or innate immune system and the development of CRS, as has been suggested by studies from our laboratory and others.[38,39] These disparate epithelial sites share some common epithelial structural elements, pathogens, innate immune responses, and pathways of inflammation with the nasal mucosa, and this study provides the first population-based epidemiologic evidence to suggest that patients with CRS might have increased rates of infections at epithelial sites outside the airway. We are further reassured by our use of a very conservative *P* value and the many prevalent general medical conditions, such as hypertension, hyperthyroidism, obesity, and diabetes, which are present at similar rates across groups.

Our study also suggests that there is a strong association between premorbid headaches and anxiety and CRS. In fact, the magnitude of these associations was almost similar to that of asthma and allergic rhinitis. Although it is well described that self-diagnosed sinus headaches are frequently manifestations of migraine[40] and that migraineurs are frequently told by their physicians they have "sinus headaches,"[41] we are unaware of studies that associate headache disorders with a subsequent CRS diagnosis. Although the autonomic manifestations of migraine are known, it is unclear whether these autonomic manifestations result in ostial occlusion and inflammation of the sinuses. More likely, the autonomic manifestations of migraine result in a symptom complex clinically indistinguishable from CRS, resulting in misdiagnosis, as suggested in multiple prior studies.[42-44] The significant and relatively large association with anxiety, but not depression, in subsequent CRS diagnosis is interesting because both are frequently comorbid and are components of negative affect in psychosomatic theory.[45] Extensive literature suggests that negative affect increases reporting of physical symptoms in the presence and absence of physical illness.[46] However, more recent studies suggest that anxiety and depression affect symptom reporting in different ways, with anxiety being more longitudinally stable,[47] and that anxious subjects report higher levels of experienced symptoms than subjects with a depressive affect.[48] Thus in a disease like CRS, in which symptoms are central to diagnosis and objective testing is still underused, symptom reporting can substantially alter the likelihood of diagnosis.

TABLE III. Associations of premorbid conditions with CRS case status in 2 time windows (7-24 months and 0-6 months) before diagnosis

Premorbid condition	Patients with CRSwNP vs control subjects, aOR (95% CI)		Patients with CRSsNP vs control subjects, aOR (95% CI)	
	7-24 mo	0-6 mo	7-24 mo	0-6 mo
Upper airway				
Acute rhinosinusitis	2.4 (2.0-2.8)*	4.6 (3.8-5.7)*	2.9 (2.7-3.1)*	7.5 (6.8-8.2)*
Otitis media	2.2 (1.6-3.0)*	3.0 (2.1-4.5)*	1.9 (1.7-2.1)*	3.4 (2.9-3.9)*
Acute URI	1.5 (1.2-1.9)*	2.0 (1.5-2.7)*	1.8 (1.7-1.9)*	2.9 (2.6-3.2)*
Allergic rhinitis	3.0 (2.4-3.7)*	5.4 (4.4-6.8)*	2.3 (2.1-2.5)*	3.7 (3.3-4)*
Chronic rhinitis	3.0 (2.1-4.3)*	8.0 (5.5-11.7)*	2.8 (2.4-3.3)*	6.1 (4.8-7.6)*
Postnasal drip	1.7 (1.3-2.2)*	2.1 (1.5-2.8)*	2.0 (1.8-2.2)*	3.2 (2.9-3.6)*
Adenotonsillitis	4.0 (1.5-10.5)	3.2 (0.7-14.4)	2.6 (1.7-4.0)*	3.7 (2.2-6.4)*
Sleep apnea	1.7 (0.8-3.2)	2.9 (1.5-5.7)	1.5 (1.1-2.0)	1.8 (1.3-2.7)*
Lower aerodigestive tract				
Asthma	3.2 (2.5-4.0)*	4.4 (3.4-5.6)*	1.8 (1.6-2.0)*	2.5 (2.2-2.9)*
Pneumonia	1.6 (0.9-2.7)	0.8 (0.3-2.1)	1.9 (1.6-2.4)*	2.7 (2.1-3.5)*
Bronchitis	1.4 (1.1-1.8)	1.6 (1.2-2.3)	1.8 (1.6-1.9)*	2.8 (2.4-3.2)*
GERD	1.5 (1.2-1.9)*	1.5 (1.1-2.0)	1.7 (1.6-1.9)*	1.8 (1.6-2.0)*
Influenza	1.7 (0.4-7.5)	1.5 (0.6-3.5)	1.5 (1.0-2.1)	2.7 (1.5-4.7)*
Epithelial conditions				
Conjunctivitis	1.5 (0.8-2.7)	2.5 (1.2-5.2)	1.7 (1.4-2.1)*	2.0 (1.5-2.7)*
UTI	1.3 (0.8-2.0)	1.2 (0.6-2.1)	1.5 (1.3-1.8)*	1.4 (1.1-1.8)
Atopic dermatitis	3.2 (1.7-6.0)*	4.2 (1.6-11.1)	1.7 (1.3-2.2)*	2.9 (1.9-4.5)*
Psoriasis	1.9 (1.0-3.8)	0.3 (0.0-2.6)	1.0 (0.7-1.5)	1.3 (0.8-2.0)
Inflammatory bowel disease	0.5 (0.1-2.1)	1.2 (0.4-4.1)	1.4 (1.0-2.1)	1.7 (1.1-2.8)
Skin/soft tissue infections	1.1 (0.8-1.5)	1.1 (0.7-1.9)	1.1 (1.0-1.3)	1.4 (1.2-1.7)
Systemic autoimmune disease				
Systemic lupus eythematosus	1.7 (0.2-13.5)	1.3 (0.6-3.0)	2.1 (0.9-4.7)	1.4 (1.0-2.0)
Rheumatoid arthritis	0.7 (0.2-2.2)	1.2 (0.5-3.0)	1.5 (1.1-2.1)	1.2 (0.9-1.9)
Other selected general medical conditions				
Diabetes mellitus	0.8 (0.6-1.0)	0.7 (0.5-1.0)	0.9 (0.8-1.1)	1.0 (0.9-1.1)
Obesity	1.4 (1.0-1.9)	1.5 (1.0-2.1)	1.1 (1.0-1.3)	1.1 (0.9-1.3)
Tobacco use	1.3 (0.8-2.1)	1.4 (0.8-2.7)	1.6 (1.3-1.9)*	1.4 (1.0-1.8)
Pregnancy	0.4 (0.1-1.1)	0.1 (0.0-1.0)	0.6 (0.5-0.8)*	0.3 (0.2-0.5)
Selected neuropsychiatric conditions				
Anxiety	1.8 (1.2-2.7)	2.3 (1.4-4.0)	1.8 (1.5-2.2)*	1.7 (1.3-2.2)*
Depression	0.9 (0.5-1.6)	1.6 (0.9-2.8)	1.2 (1.0-1.5)	1.4 (1.1-1.8)
Headache	2.0 (1.5-2.6)*	5.3 (3.9-6.9)*	1.7 (1.5-1.9)*	3.0 (2.5-3.5)*
Other miscellaneous conditions				
Hypothyroidism	1.1 (0.8-1.5)	1.3 (1.0-1.9)	1.2 (1.0-1.3)	1.3 (1.1-1.4)
Colon cancer	0.6 (0.0-2.8)	1.0 (0.3-3.2)	0.7 (0.4-1.2)	0.5 (0.3-1.0)
Essential hypertension	0.9 (0.7-1.1)	1.0 (0.8-1.2)	1.0 (0.9-1.1)	1.2 (1.1-1.3)*
Heart failure	1.1 (0.6-2.0)	1.0 (0.5-1.9)	1.2 (0.9-1.5)	1.2 (0.9-1.6)

aOR, Adjusted odds ratio; *NC*, models did not converge.
*$P < .0005$: logistic regression was used to derive adjusted ORs and 95% CIs, controlling for race/ethnicity, sex, and age.

In our study only 24% of patients given a diagnosis of CRSsNP and 52% of patients receiving a diagnosis of CRSwNP were documented to have received nasal endoscopy or a sinus CT scan for confirmatory diagnostic testing. Testing was usually performed after diagnosis and presumably treatment, and our study highlights the low rates of guideline-recommended confirmatory diagnostic testing for CRS in the primary care setting. Despite low rates of confirmatory testing, patients with CRS receive between 2 and 3 times the number of antibiotic prescriptions received by age- and sex-matched control patients. Few previous studies have examined antibiotic use in relation to the specific site of acute URI,[49] but a National Ambulatory Medical Care Survey–based study by Steinman el al[50] estimates that for rhinosinusitis is the single most common indication for ambulatory antibiotic use, accounting for approximately 8 million antibiotic prescriptions annually. Similarly, a recent study suggested that symptom duration was the most heavily weighted variable in the community practitioner's decision to prescribe an antibiotic for a URI.[51] Thus our study emphasizes the importance of CRS care in overall antibiotic stewardship and suggests the need for vigorous dissemination of specialty guideline recommendations to the primary care setting.

Limitations of this study were that these observations were made with retrospective analysis of practitioner-coded ICD-9 codes, and subsequently, the adherence to professional society guidelines for the diagnosis of each condition could not be ensured. Furthermore, given the low rates of use of confirmatory testing for CRS, especially in patients with CRSsNP, accurate differentiation of patients with CRSwNP from patients with CRSsNP might not be possible using our current methodology. Because there exists considerable overlap in the symptoms of the 2 CRS phenotypes, as well as non-CRS diseases with overlapping symptoms, a nonspecialist physician's diagnosis of CRS might be

TABLE IV. Outpatient, inpatient, and emergency department encounters in 2 time periods before CRS diagnosis or matched visit in patients with CRS and control subjects

	0-6 mo prior				7-24 mo prior			
	Patients with CRSwNP	Patients with CRSsNP	Control subjects	*P* value*	Patients with CRSwNP	Patients with CRSsNP	Control subjects	*P* value*
Median outpatient visits	2	2	1		4	5	4	
Mean (SD) outpatient visits	2.6 (2.8)	2.9 (3.0)	1.8 (2.5)	<.0005	5.8 (6.1)	6.6 (6.9)	5.1 (5.7)	<.0005
Mean (SD) inpatient visits	0.05 (0.3)	0.08 (0.8)	0.05 (0.4)	.003	0.2 (1.1)	0.3 (1.7)	0.2 (0.8)	<.0005
Mean (SD) emergency department visits	0.01 (0.2)	0.03 (0.3)	0.02 (0.2)	.04	0.05 (0.3)	0.08 (0.8)	0.05 (0.4)	.006

**P* values are for 1-way ANOVA of the 3 groups.

TABLE V. Use, prevalence, and indication of medication orders (by physician) in 2 time windows before CRS diagnosis or control visit

	7-24 mo before CRS diagnosis				0-6 mo before CRS diagnosis			
	Patients with CRSwNP	Patients with CRSsNP	Control subjects	*P* value*	Patients with CRSwNP	Patients with CRSsNP	Control subjects	*P* value*
Overall antibiotic use								
No, of orders, mean (SD)	1.5 (2.4)	1.7 (2.3)	0.9 (1.7)	<.0005	0.9 (1.7)	1.1 (1.5)	0.4 (1.0)	<.0005
Antibiotic for any indication	53.8%	59.5%	42.3%	<.0005	43.0%	54.0%	22.3%	<.0005
Most common indications for antibiotic prescription (% of patients who received medication for indication)								
Acute rhinosinusitis	29.1%	35.5%	16.3%	<.0005	24.9%	35.8%	7.2%	<.0005
Bronchitis	10.9%	13.6%	8.3%	<.0005	5.9%	8.1%	3.2%	<.0005
URI	7.7%	9.6%	5.7%	<.0005	3.7%	4.8%	1.6%	<.0005
Other selected indications								
Otitis media	5.7%	10.8%	6.3%	<.0005	3.2%	6.9%	2.2%	<.0005
Skin/soft tissue infection	5.2%	5.2%	4.5%	.091	1.5%	2.4%	1.8%	.041
UTI	2.9%	3.4%	2.3%	<.0005	1.7%	1.6%	1.1%	<.0005
Pneumonia	0.7%	2.0%	0.9%	<.0005	0.8%	1.7%	0.6%	<.0005
Overall nasal steroid use								
No. of orders, mean (SD)	0.3 (1.0)	0.3 (1.0)	0.2 (0.7)	<.0005	0.3 (0.6)	0.2 (0.5)	0.0 (0.2)	<.0005
Nasal steroid for any indication	20.8%	18.3%	7.3%	<.0005	18.6%	14.6%	3.1%	<.0005
Most common indications for nasal steroid prescription (% of patients who received medication for indication)								
Allergic rhinitis	12.8%	9.4%	3.8%	<.0005	11.6%	7.0%	1.8%	<.0005
Acute rhinosinusitis	4.8%	5.7%	1.5%	<.0005	3.7%	4.8%	0.7%	<.0005
Chronic rhinitis	4.0%	3.3%	1.3%	<.0005	3.2%	2.5%	0.5%	<.0005
Overall systemic steroid use								
No. of orders, mean (SD)	0.4 (0.9)	0.3 (0.7)	0.1 (0.4)	<.0005	0.2 (0.7)	0.2 (0.6)	0.1 (0.4)	<.0005
Systemic steroid for any indication	14.8%	11.6%	5.5%	<.0005	10.6%	11.1%	2.4%	<.0005
Indication for systemic steroid prescription (% of patients who received medication for indication)								
Asthma	5.9%	2.9%	1.2%	<.0005	3.2%	2.8%	0.6%	<.0005
Bronchitis	3.5%	2.7%	1.6%	<.0005	1.7%	2.5%	0.6%	<.0005
Acute rhinosinusitis	2.5%	1.7%	0.5%	<.0005	2.5%	2.4%	0.2%	<.0005

*For continuous variables, *P* values are based on the F test from ANOVA for differences between the means; for categorical variables, *P* values are based on the Pearson χ^2 test for association.

TABLE VI. Prevalence of confirmatory diagnostic test use in patients given a diagnosis of CRSwNP, patients given a diagnosis of CRSsNP, and control subjects in time windows before or after diagnosis

	CPT codes	Patients with CRSwNP	Patients with CRSsNP	Control subjects	*P* value
Sinus CT ever (%)	70486	195 (32.8%)	1,274 (16.9%)	93 (1.2%)	<.0005
Up to 1 y before		11.6%	2.5%	0.3%	
Within 3 mo after diagnosis		15.3%	11.0%	0%	
Upper airway endoscopy ever (%)	31231, 31575, 92511	371 (37.7%)	1,014 (13.5%)	212 (2.6%)	<.0005
Up to 1 y before		6.9%	1.4%	0.4%	
Within 3 mo after diagnosis		19.5%	4.1%	0.1%	
Endoscopy or CT ever (%)		308 (51.8%)	1,820 (24.2%)	294 (3.6%)	<.0005
Endoscopy and CT ever (%)		111 (18.7%)	468 (6.2%)	11 (0.1%)	<.0005

insufficient to accurately define this disease.[52,53] Inaccurate differentiation between CRS phenotypes and non-CRS diseases with similar symptoms might explain the few differences we find in the premorbid patterns of illness among patients with CRSwNP and patients with CRSsNP. However, we believe these concerns are mitigated by our large longitudinal dataset that is

sampled from a population with low attrition served by a single primary care–focused health care organization. Together, these data likely reflect the current state of CRS care as practiced in the real-world, primary care setting.

Clinical implications: Patients with CRS have an increased premorbid prevalence of inflammatory and infectious conditions of the airway and other epithelial barriers, GERD, and sleep apnea. Compliance with guideline recommendations for accurate diagnosis of CRS is low.

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